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Volumetric and viscometric studies of cefepime hydrochloride in water and normal saline from (278.15 to 313.15) K

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ABSTRACT

Density (ρ) and viscosity (η) measurements were carried out for cefepime hydrochloride in water and 0.9 mass % normal saline from (278.15 to 313.15) K. The dependence of density and viscosity on temperature and concentration has been correlated. Apparent molar volumes, standard partial molar volumes, and the viscosity *B*-coefficient of cefepime hydrochloride were calculated from the experimental measurements. The results are used to establish the nature of solute–solute. Solute–solvent interactions and structure breaking effect of cefepime hydrochloride have been discussed using the Helper equation and the Jones–Dole equation. The relationship between relative changes in viscosity and solute-mixed solvent interaction has been probed.

1. Introduction

Drugs play an important role in human health and livestock rearing. Physicochemical properties of drugs are of great benefits to understand the drug action at the molecular level. The pharmadynamics and pharmakinetics [1], such as the transmission, diffusion, distribution and absorption of the drug in vivo, must be regarded as the ultimate consequence of physicochemical interactions between the drug and functionally important molecules in the living organism [2]. The interactions may include ionic or covalent, charge transfer, hydrogen bonding, ion–dipole interactions, or hydrophobic interactions [3]. Moreover, the unabsorbed drug or its metabolites may enter the water via urine, fecal excretion, etc. [4,5], which will contaminate the water. In recent years, the wide application of drugs has led to be large presence in environment. The migration, transformation of drugs and the potential ecological and health risks in environment has become a subject of interest in the field of international environment [6,7].

Since most of the biochemical processes occur in aqueous media, the studies on the thermodynamic and transport properties of drugs, such as volumetric and viscometric properties, in the aqueous phase provides useful information in pharmaceutical and medicinal chemistry. The drug–water molecular interaction and their temperature dependence play an important role in the understanding of drug action [8]. Therefore, such results can be helpful to predict the absorption of drugs and transport of drugs across the biological membranes, it is also essential to investigate the presence, migration and transformation of the drugs in environment.

Cefepime hydrochloride is a semisynthetic, broad spectrum fourth-generation cephalosporin antibiotic and widely applied in clinical practice [9–11]. Sodium chloride is mainly in the extracellular fluid and necessary for human life. It plays an important role in maintaining the balance of osmotic pressure and electrolyte of body fluids. Therefore, the electrolyte influences the stability of biomolecules greatly [12,13]. The solution is often regarded as a typical electrolyte solution and crucial in the biochemical system [14]. The detailed literature survey reveals that the information is scant on the volumetric and viscometric characteristics of cefepime hydrochloride. Thus, we planned to carry out the volumetric and viscometric studies on cefepime hydrochloride in water and aqueous solutions of sodium chloride at different temperature.

The present study is a continuation of our earlier work on cephalosporins [15]. In this paper, 0.9 mass % normal saline is regarded as simulated biological solutions, the density (ρ) and viscosity (η) data of cefepime hydrochloride in water and 0.9 mass % normal saline from (278.15 to 313.15) K are reported. From experimental data, apparent molar volumes, standard partial molar volumes,

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and the viscosity *B*-coefficient of cefepime hydrochloride were calculated. The solute–solute and solute–solvent interactions occurring in the binary (cefepime hydrochloride + water) and ternary (cefepime hydrochloride + 0.9 mass % normal saline) systems and the structure making/breaking tendency of the solutes in the given solvent have been discussed. The study can be helpful to understand the nature of biochemical process and structure effect of bio-fluids in the body-system, and the migration, transformation of cefepime hydrochloride in enviroment.

2. Experimental section

2.1. Materials

Cefepime dihydrochloride hydrate ($C_{19}H_{24}N_6O_5S_2 \cdot 2HCl \cdot H_2O$, molecular weight 571.49) was purchased from Haikou Manfangyuan Chemical Co. Ltd., China and purified by recrystallization. Its mass fraction purity was better than 0.99, which was determined by HPLC (type Agilent 1200, Agilent Technologies) according to the JP 15th Edition [16]. It was dried in vacuum at 313.15 K for 24 h and stored in a desiccator. NaCl was of AR grade, which was obtained from Tianjin Kermel Chemical Reagent Co., Ltd, China and its purity was greater than 0.997 by mass. It was dried at 823.15 K for 1 h in a 1100 °C Mini chamber electric lab furnace (SXL-1100M, Shanghai Daheng Optics and Fine Mechanics Co., Ltd) and stored in a desiccator. The distillated deionized water with a conductivity less than $1 \cdot 10^{-4}\ S \cdot m^{-1}$ was used in our experiments. It was degassed by boiling prior to making solutions. All the solutions were prepared in freshly distillated deionized water on a molality basis and converted to the molarity scale when required, using density data at different temperatures. A Mettler balance (MS205DU, ±0.00001 g) was used for weighing. The detailed information of the materials used in this experiment is listed in table 1.

2.2. Apparatus and procedure

The densities (ρ) of the solutions were measured to $\pm 1 \cdot 10^{-2}$ - $kg \cdot m^{-3}$ using a vibrating-tube digital densimeter (DMA 60/602, Anton Paar, Austria) that was calibrated at each investigated temperature using dry air and conductivity water daily. The densities of pure water were taken from Lange's Handbook of Chemistry [17] and listed in table 2. The temperature around the densimeter cell was controlled by circulating water from a constant-temperature bath (±0.005 K, Schott, Germany).

Viscosity was measured by means of a suspended level Ubbelhode viscometer (type 1836-A, Shanghai Glass Instruments Factory, China) with a flow time of approximately 200 s for distilled water at 308.15 K. The time of flow was measured with a stop watch capable of recording ±0.01 s. The viscometer was also calibrated with distillated deionized water at (278.15, 283.15, 288.15, 293.15, 298.15, 303.15, 308.15, and 313.15) K. An average of three to four sets of flow time for each solution was taken for the calculation of viscosity. The overall experimental uncertainty was estimated to be $\pm 1.5 \cdot 10^{-6}$ Pa · s. As the flow times were greater than 200 s, and the capillary diameter (0.55 mm) was far less than its length (90–100 mm), the kinetic energy and end corrections, respectively, were found to be negligible [18]. The Ubbelhode viscometer filled with test solutions was allowed to stand for about 30 min in a thermostatic water bath (type DC-2006, Shanghai Bilon Instruments Co., Ltd., China) so as to minimize thermal fluctuations (±0.05 K).

The viscosity (η) was then calculated from the relationship [13]

$$\eta/\eta_w = \rho t/(\rho_w t_w), \tag{1}$$

where η (Pa · s), ρ ($kg \cdot m^{-3}$), t (s) and η_w (Pa · s), ρ_w ($kg \cdot m^{-3}$), t_w (s) are the viscosity, density, and flow time of the mixture and pure water, respectively. The viscosities of pure water were taken from Lange's Handbook of Chemistry [17] and listed in table 2. The uncertainty of the viscosity measurement is estimated to be ±0.6% at the 95% confidence level on the basis of the principle of error propagation.

3. Results and discussion

The experimental densities and viscosities for cefepime hydrochloride + water binary mixtures and cefepime hydrochloride + 0.9 mass % normal saline ternary mixtures at the temperatures from (278.15 to 313.15) K are listed in tables 3 and 4, respectively. It can be found that the density and viscosity decrease with increasing temperature at a certain concentration, and increase with increasing concentration of cefepime hydrochloride at a constant temperature. The increase of the viscosity caused by the increase of the concentration can be simply explained by the use of the Einstein equation [19]:

$$n = n_0(1 + 2.5f_i), \tag{2}$$

where n is the viscosity of the solution, n_0 is the viscosity of the pure solvent, f_i is the volume fraction of the solute. This increase of the viscosity is often related to the dissipation of the hydrodynamic energy due to distortion of the flow in the vicinity of the solute.

3.1. Correlation of density and viscosity

The dependence of density and viscosity on temperature and concentration has been correlated by means of the Vogel–Tamman–Fulcher equation [20,21].

$$Y = P_1 \exp\left(\frac{P_2 + P_3 m}{T - P_4}\right), \tag{3}$$

where Y represents ρ or η, ρ ($kg \cdot m^{-3}$) and η (Pa · s) are the density and viscosity of solution, respectively; m ($mol \cdot kg^{-1}$) is the molality of cefepime hydrochloride in the solutions; T (K) is the absolute temperature; P_1, P_2, P_3 and P_4 are the curve-fit coefficients. The values of coefficients are listed in table 5, along with the standard deviations (SD) and average relative deviations (ARD) of the estimate. The standard deviations (SD) and average relative deviations (ARD) are defined as

$$SD = \left(\sum (Y_i^{exp} - Y_i^{cal})^2/(p - n)\right)^{1/2}, \tag{4}$$

TABLE 1
Specification of chemical samples.

Compounds	Mass fraction purity	Source	Purification method	Analysis method
$C_{19}H_{24}N_6O_5S_2 \cdot 2HCl \cdot H_2O$	0.995	Haikou Manfangyuan Chemical Co. Ltd., China	Recrystallization	HPLC
NaCl (AR)	0.997	Tianjin Kermel Chemical Reagent Co., Ltd, China		
Water	0.999	Self made		

* AR means analytical reagent; HPLC means high performance liquid chromatography.

TABLE 2
Densities (ρ) and viscosities (η) of water from T (278.15 to 313.15) K.

T/K	278.15	283.15	288.15	293.15	298.15	303.15	308.15	313.15
ρ_0/kg · m^{-3}	999.96	999.70	999.10	998.20	997.05	995.65	994.04	992.22
$10^3 \cdot \eta_0$/Pa · s	1.521	1.307	1.135	1.002	0.8903	0.7977	0.7190	0.6532

TABLE 3
Experimental densities (ρ),[a] viscosities (η)[b] and apparent molar volume (V_φ) of cefepime hydrochloride + water binary mixture as a function of molality of cefepime hydrochloride, m, from T (278.15 to 313.15) K.

m/mol · kg^{-1}	$10^{-3} \cdot \rho$/kg · m^{-3}	$10^6 \cdot V_\varphi$/m^3 · mol^{-1}	$10^3 \cdot \eta$/Pa · s	$10^{-3} \cdot \rho$/kg · m^{-3}	$10^6 \cdot V_\varphi$/m^3 · mol^{-1}	$10^3 \cdot \eta$/Pa · s
		T = 278.15 K			*T = 283.15 K*	
0	0.99996		1.5210	0.99970		1.3070
0.01005	1.00200	367.76	1.5437	1.00173	368.80	1.3237
0.02017	1.00401	369.21	1.5698	1.00373	370.25	1.3478
0.03040	1.00602	369.91	1.5975	1.00573	370.95	1.3714
0.05103	1.00998	371.42	1.6488	1.00967	372.45	1.4157
0.07222	1.01397	372.29	1.7053	1.01362	373.60	1.4632
0.09333	1.01786	373.03	1.7663	1.01747	374.49	1.5168
0.1154	1.02184	373.72	1.8241	1.02140	375.36	1.5660
0.1343	1.02519	374.19	1.8795	1.02471	375.92	1.6130
0.1521	1.02829	374.63	1.9370	1.02779	376.30	1.6635
		T = 288.15 K			*T = 293.15 K*	
0	0.99910		1.1350	0.99820		1.0020
0.01005	1.00111	370.90	1.1483	1.00020	372.05	1.0127
0.02017	1.00310	371.84	1.1696	1.00218	373.00	1.0314
0.0304	1.00508	372.71	1.1899	1.00415	373.86	1.0490
0.05103	1.00898	374.34	1.2276	1.00803	375.50	1.0821
0.07222	1.01289	375.53	1.2692	1.01191	376.82	1.1197
0.09333	1.01670	376.46	1.3160	1.01570	377.72	1.1611
0.1154	1.02061	377.15	1.3590	1.01957	378.57	1.1991
0.1343	1.02389	377.71	1.4002	1.02282	379.19	1.2351
0.1521	1.02693	378.17	1.4432	1.02583	379.70	1.2726
		T = 298.15 K			*T = 303.15 K*	
0	0.99705		0.8903	0.99565		0.7977
0.01005	0.99904	372.95	0.8990	0.99763	374.50	0.8046
0.02017	1.00101	374.20	0.9159	0.99959	375.45	0.8192
0.03040	1.00297	375.06	0.9314	1.00153	376.65	0.8325
0.05103	1.00684	376.50	0.9593	1.00538	377.95	0.8581
0.07222	1.01070	377.88	0.9939	1.00921	379.42	0.8888
0.09333	1.01446	378.92	1.0293	1.01295	380.39	0.9175
0.1154	1.01829	379.94	1.0650	1.01675	381.46	0.9513
0.1343	1.02151	380.63	1.0964	1.01994	382.21	0.9813
0.1521	1.02450	381.14	1.1299	1.02290	382.78	1.0096
		T = 308.15 K			*T = 313.15 K*	
0.0000	0.99404		0.7190	0.99222		0.6532
0.01005	0.99601	375.79	0.7235	0.99418	377.13	0.6561
0.02017	0.99796	376.75	0.7352	0.99612	378.08	0.6652
0.03040	0.99990	377.61	0.7465	0.99804	379.28	0.6753
0.05103	1.00371	379.45	0.7718	1.00185	380.59	0.6976
0.07222	1.00753	380.71	0.7974	1.00564	382.06	0.7193
0.09333	1.01124	381.80	0.8261	1.00933	383.15	0.7448
0.1154	1.01502	382.85	0.8553	1.01307	384.37	0.7705
0.1343	1.01818	383.69	0.8810	1.01622	385.14	0.7947
0.1521	1.02112	384.27	0.9040	1.01914	385.73	0.8162

The experimental pressure is 101.33 kPa.
[a] Standard uncertainty σ are $\sigma(T) = \pm 0.005$ K; $\sigma(m) = \pm 0.0001$ mol · kg^{-1}; $\sigma(\rho) = \pm 1 \cdot 10^{-2}$ kg · m^{-3}.
[b] Standard uncertainty σ are $\sigma(T) = \pm 0.05$ K; $\sigma(m) = \pm 0.0001$ mol · kg^{-1}; $\sigma(\eta) = \pm 1.5 \cdot 10^{-6}$ Pa · s.

$$\mathrm{ARD} = \frac{1}{p} \sum \frac{|Y_i^{\mathrm{cal}} - Y_i^{\mathrm{exp}}|}{Y_i^{\mathrm{exp}}}, \tag{5}$$

where p is the number of data points and n is the number of coefficients. Y_i^{cal} and Y_i^{exp} refer to the calculated values using equation (3) and the experimental values, respectively. The densities and viscosities of cefepime hydrochloride + water binary mixture and cefepime hydrochloride + 0.9 mass % normal saline ternary mixture were calculated according to equation (3) using parameters P_1, P_2, P_3 and P_4 are listed in table 5. Comparing the calculated values with experimental values, for densities, the total SD and ARD of 152 points are 9.4 kg · m^{-3} and 0.73%, respectively. For viscosities, those are $6.7 \cdot 10^{-6}$ Pa · s and 0.46%, respectively. It is clear that equation (3) can be successfully used to correlate densities and viscosities of cefepime hydrochloride + water binary mixture and cefepime hydrochloride + 0.9 mass % normal saline ternary mixture.

3.2. Apparent molar volume

The apparent molar volumes and partial molar volumes of solutes in solvent systems can be calculated using the density data,

TABLE 4
Experimental densities (ρ)[a], viscosities (η)[b] and apparent molar volume (V_φ) of cefepime hydrochloride + 0.9 mass % normal saline ternary mixture as a function of molality of cefepime hydrochloride, m, from T (278.15 to 313.15) K.

m/mol · kg^{-1}	$10^{-3}\cdot\rho$/kg · m^{-3}	$10^{6}\cdot V_\varphi$/m^3 · mol^{-1}	$10^{3}\cdot\eta$/Pa · s	$10^{-3}\cdot\rho$/kg · m^{-3}	$10^{6}\cdot V_\varphi$/m^3 · mol^{-1}	$10^{3}\cdot\eta$/Pa · s
	T = 278.15 K			*T = 283.15 K*		
0	1.00609		1.5296	1.00564		1.3206
0.01000	1.00834	344.97	1.5562	1.00787	347.01	1.3427
0.03022	1.01242	358.84	1.6032	1.01193	360.22	1.3837
0.05077	1.01636	364.47	1.6627	1.01581	366.50	1.4303
0.07166	1.02020	368.34	1.7113	1.01962	370.23	1.4755
0.09279	1.02399	370.85	1.7707	1.02340	372.45	1.5285
0.1143	1.02783	372.08	1.8358	1.02720	373.76	1.5804
0.1354	1.03158	372.61	1.8869	1.03090	374.41	1.6262
0.1535	1.03473	373.08	1.9388	1.03400	375.02	1.6721
	T = 288.15 K			*T = 293.15 K*		
0	1.00507		1.1543	1.00414		1.0155
0.01000	1.00728	349.06	1.1720	1.00633	351.17	1.0301
0.03022	1.01131	361.95	1.2082	1.01032	364.08	1.0613
0.05077	1.01516	368.17	1.2485	1.01414	370.10	1.0972
0.07166	1.01893	372.01	1.2890	1.01788	373.86	1.1325
0.09279	1.02265	374.50	1.3340	1.02157	376.30	1.1727
0.1143	1.02639	375.98	1.3802	1.02528	377.75	1.2126
0.1354	1.03006	376.54	1.4204	1.02891	378.37	1.2489
0.1535	1.03314	377.05	1.4600	1.03194	379.02	1.2848
	T = 298.15 K			*T = 303.15 K*		
0	1.00296		0.90675	1.00147		0.81049
0.01000	1.00513	353.32	0.91890	1.00362	355.52	0.81981
0.03022	1.00910	365.59	0.94710	1.00757	367.15	0.84526
0.05077	1.01288	371.89	0.97890	1.01132	373.53	0.87306
0.07166	1.01657	375.90	1.0109	1.01499	377.44	0.90183
0.09279	1.02022	378.38	1.0461	1.01862	379.86	0.93352
0.1143	1.02389	379.84	1.0821	1.02228	381.20	0.96594
0.1354	1.02749	380.40	1.1134	1.02586	381.75	0.99228
0.1535	1.03049	381.05	1.1467	1.02889	382.08	1.0228
	T = 308.15 K			*T = 313.15 K*		
0	0.99975		0.73632	0.99782		0.66409
0.01000	1.00189	357.06	0.74324	0.99994	359.05	0.66887
0.03022	1.00580	369.20	0.76518	1.00384	370.53	0.68866
0.05077	1.00955	374.89	0.79221	1.00756	376.44	0.71224
0.07166	1.01321	378.65	0.81687	1.01118	380.44	0.73488
0.09279	1.01682	381.10	0.84485	1.01478	382.69	0.75686
0.1143	1.02049	382.19	0.87202	1.01843	383.74	0.78449
0.1354	1.02401	383.10	0.90045	1.02195	384.47	0.81065
0.1535	1.02700	383.58	0.92563	1.02490	385.12	0.83044

The experimental pressure is 101.33 kPa.
[a] Standard uncertainty σ are $\sigma(T) = \pm 0.005$ K; $\sigma(m) = \pm 0.0001$ mol · kg^{-1}; $\sigma(\rho) = \pm 1\cdot 10^{-2}$ kg · m^{-3}.
[b] Standard uncertainty σ are $\sigma(T) = \pm 0.05$ K; $\sigma(m) = \pm 0.0001$ mol · kg^{-1}; $\sigma(\eta) = \pm 1.5\cdot 10^{-6}$ Pa · s.

TABLE 5
Coefficients of equation (3), together with standard deviation (SD) and average relative deviations (ARD) for the density (ρ) and viscosity (η) in different systems.

	P_1	P_2	P_3	P_4	SD	10 · ARD%
			Cefepime hydrochloride + H_2O			
Density (ρ)	1.0096	0.0024	−0.0360	298.35	9.39 kg · m^{-3}	7.39
Viscosity (η)	0.0187	659.34	250.06	127.80	6.79 · 10^{-6} Pa · s	4.36
			Cefepime hydrochloride + 0.9 mass % normal saline			
Density (ρ)	1.0165	0.0026	−0.0363	298.36	9.48 kg · m^{-3}	7.32
Viscosity (η)	0.0238	594.07	235.36	135.16	6.86 · 10^{-6} Pa · s	5.41

which can explain solvent–solvent and drug/solute–solvent interactions in turn [22,23].

The apparent molar volume (V_φ) of cefepime hydrochloride in cefepime hydrochloride + water binary mixture and cefepime hydrochloride + 0.9 mass % normal saline ternary mixtures is given by the following equation [20].

$$V_\varphi = \frac{M}{\rho} - \frac{10^3(\rho-\rho_0)}{m\rho\rho_0}, \tag{6}$$

in which M and m are the molar mass and molality of cefepime hydrochloride, respectively. ρ is the density of the solution, and ρ_0 is the density of the solvent. Values of the apparent molar volume of cefepime hydrochloride in water or 0.9 mass % normal saline mixed solvent have also been given in tables 3 and 4, respectively. These values are important because they form the basis for understanding molecular interactions. It can be found that the apparent molar volume (V_φ) increase with increasing both temperature of the solutions and concentration of cefepime hydrochloride at a constant temperature. It also can be seen that the apparent molar

TABLE 6
Limiting partial molar volume (V^0_φ), parameter (A_V), experimental constant (B_V) and limiting partial molar volume expansibility ($(\partial V^0_\varphi/\partial T)_p$) of cefepime hydrochloride in water or 0.9 mass % normal saline mixed solvent at the indicated temperatures.

T/K	$10^6 \cdot V^0_\varphi/m^{-3} \cdot mol^{-1}$	$10^6 \cdot A_V/m^{-3} \cdot kg^{1/2} \cdot mol^{-3/2}$	$10^6 \cdot B_V/m^{-3} \cdot mol^{-1}$	$10^6 \cdot (\partial V^0_\varphi/\partial T)_p/m^3 \cdot mol^{-1} \cdot K^{-1}$
		Cefepime hydrochloride + water		
278.15	364.41	36.860	−27.633	0.2936
283.15	365.49	35.185	−18.686	0.2909
288.15	367.48	32.044	−16.384	0.2882
293.15	368.77	31.908	−9.7279	0.2855
298.15	369.89	30.613	−3.8763	0.2828
303.15	371.47	29.201	0.0060	0.2801
308.15	372.75	28.491	3.3770	0.2774
313.15	374.27	26.915	7.1257	0.2747
		Cefepime hydrochloride + 0.9 mass % normal saline		
278.15	321.71	269.86	−356.02	0.4984
283.15	324.11	266.48	−351.32	0.4919
288.15	326.50	260.97	−338.41	0.4854
293.15	329.04	256.76	−331.95	0.4789
298.15	331.33	252.65	−322.39	0.4724
303.15	333.86	247.83	−318.81	0.4659
308.15	336.10	242.41	−311.09	0.4594
313.15	338.29	238.34	−304.99	0.4529

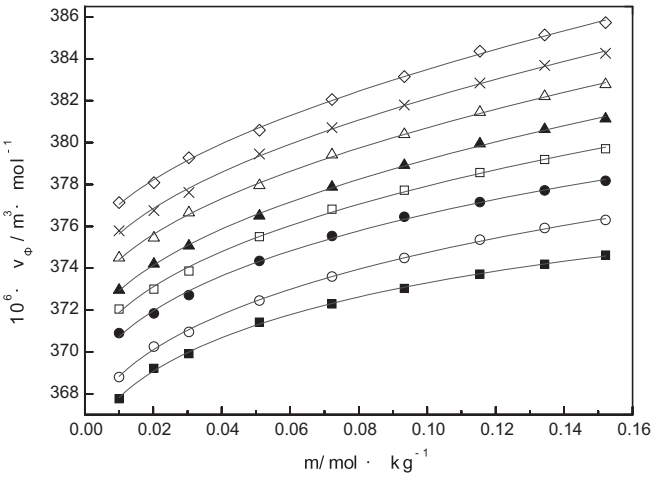

FIGURE 1. Plot of dependencies of the partial molar volume (V_φ) on molality cefepime hydrochloride (m) for cefepime hydrochloride + water binary mixtures (T = ■, 278.15 K; ○, 283.15 K; ●, 288.15 K; □, 293.15 K; ▲, 298.15 K; △, 303.15 K; ×, 308.15 K; ◇, 313.15 K).

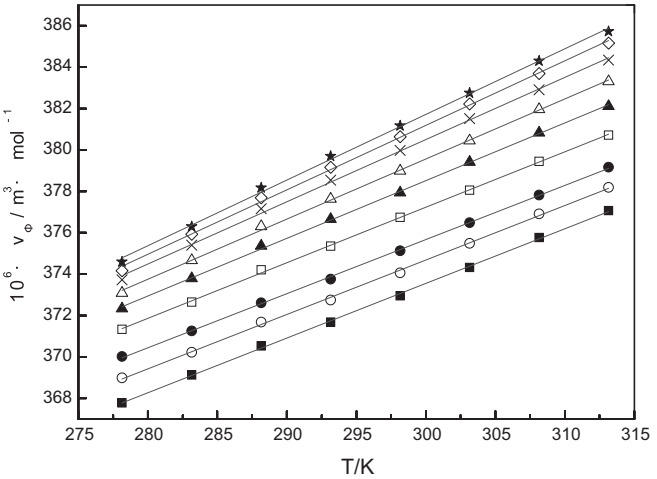

FIGURE 2. Plot of dependencies of the partial molar volume (V_ϕ) on temperature (T) for cefepime hydrochloride + water binary mixtures (m/mol · kg^{-1} = ■, 0.01005; ○, 0.02017; ●, 0.03040; □, 0.05103; ▲, 0.07222; △, 0.09333; ×, 0.1154; ◇, 0.1343; ★, 0.1521).

volume (V_φ) of solute in solute + water binary mixture are greater than the values of solute in cefepime hydrochloride + 0.9 mass % normal saline ternary mixtures. This may be explained by the following reasons [24]. Cefepime hydrochloride (A) molecule not only contains a large substituent with both basic group (–NH_2) and acidic groups (–COOH), but also contains complex group with different characteristics such as methylpyridinium. The solute molecules contain hydrophilic groups, such as –NH_2, –COOH, also contain hydrophobic groups such as –CH_3, and so forth. Because the NaCl is highly hydrophilic in aqueous solution, and its hydrophilic is higher than that of cefepime hydrochloride, to some extent, addition of NaCl in aqueous solution of cefepime hydrochloride reduced the hydrophilic cefepime hydrochloride molecule. The effect led to the increase of hydrophobic ability of solute, and resulted in the decrease of the apparent molar volume of cefepime hydrochloride in cefepime hydrochloride + 0.9 mass % normal saline ternary mixtures [25].

Concentration of solute effect on the apparent molar volume reflects interactions between solute molecules. When concentration of solute tends to zero, the limiting apparent molar volume manifests interactions between solute and solvent, which is equal in value to the standard partial molar volume embodies the solute and solvent interactions.

The dependence of the apparent molar volume (V_φ) of cefepime hydrochloride in water or 0.9 mass % normal saline mixed solvent on its molality at a definite temperature can be analyzed by fitting to the following equation [20,25].

$$V_\varphi = V^0_\varphi + A_V \cdot m^{1/2} + B_V \cdot m, \tag{7}$$

where V^0_φ ($m^3 \cdot mol^{-1}$) represents the apparent molar volume of solute at infinite dilution, equal to the limiting partial molar volume of solute; A_V ($m^3 \cdot kg^{1/2} \cdot mol^{-3/2}$) is an empirical parameter; B_V is the experimental constant which depends on solute, solvent and temperature. The values of V^0_φ, A_V and B_V obtained from experimental data by least-squares analysis, are listed in table 6. The dependencies of the partial molar volume (V_ϕ) on molality cefepime hydrochloride (m) or different temperatures (T) for cefepime

TABLE 7
Values of constants (a_i) and the standard deviation of equation (8) and the term $(\partial^2 V_\varphi^0/\partial T^2)_P$ for cefepime hydrochloride in water or 0.9 mass % normal saline mixed solvent.

	a_0	$10 \cdot a_1$	$10^4 \cdot a_2$	SD	$10^4(\partial^2 V_\varphi^0/\partial T^2)_P$
Cefepime hydrochloride + water	257.03	4.7638	−3.3000	0.474	−6.60
Cefepime hydrochloride + 0.9 mass % normal saline	132.54	8.6003	−6.5000	0.280	−13.0

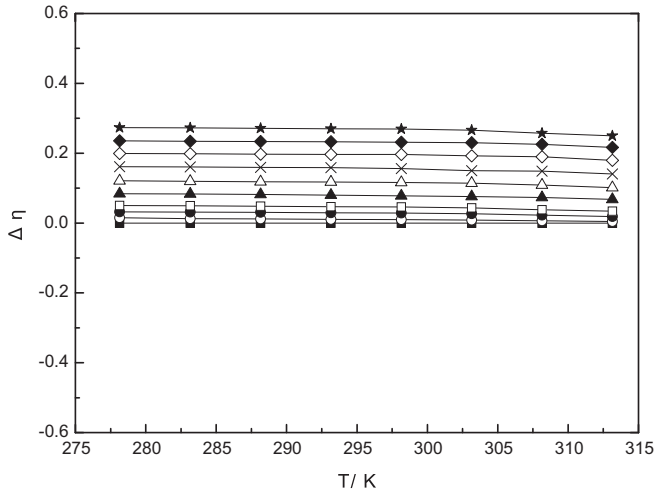

FIGURE 3. Plot of the relative changes of viscosity ($\Delta\eta$) versus temperature (T) for cefepime hydrochloride + water binary mixtures (c/mol · l^{-1} = ■, 0; ○, 0.01005; ●, 0.02021; □, 0.03053; ▲, 0.05144; △, 0.07308; ×, 0.09480; ◇, 0.1177; ♦, 0.1374, ★, 0.1560).

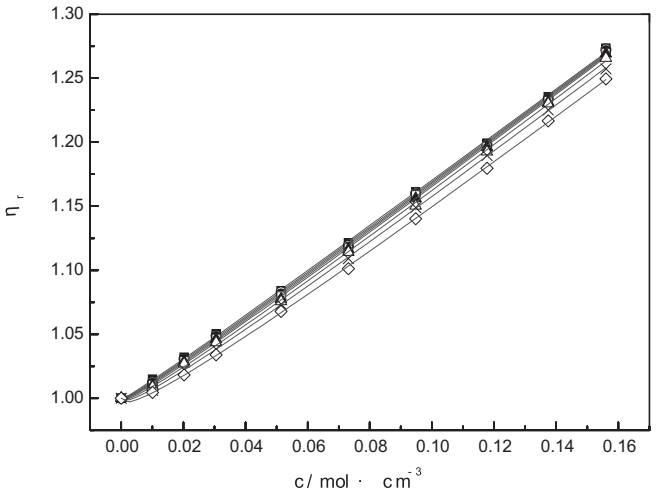

FIGURE 4. Plot of dependencies of relative changes in viscosity (η_r) on molarity cefepime hydrochloride (c) for cefepime hydrochloride + water binary mixtures (T = ■, 278.15 K; ○, 283.15 K; ●, 288.15 K; □, 293.15 K; ▲, 298.15 K; △, 303.15 K; ×, 308.15 K; ◇, 313.15 K).

TABLE 8
Viscosity B-coefficient of cefepime hydrochloride in water or 0.9 mass % normal saline mixed solvent at the indicated temperatures.

T/K	$10^2 \cdot A$	$10^3 \cdot B$/m$^3 \cdot$ mol^{-1}	$10^2 \cdot A$	$10^3 \cdot B$/m$^3 \cdot$ mol^{-1}
	Cefepime hydrochloride + water		*Cefepime hydrochloride + 0.9 mass % normal saline*	
278.15	−4.4580	1.8447	−1.9440	1.7373
283.15	−5.6660	1.8673	−3.0860	1.7540
288.15	−6.4150	1.8870	−4.0970	1.7730
293.15	−7.3240	1.9076	−5.5560	1.8085
298.15	−8.5770	1.9295	−6.0770	1.8153
303.15	−10.465	1.9529	−7.3610	1.8311
308.15	−12.739	1.9750	−9.3520	1.8538
313.15	−16.081	1.9955	−11.241	1.8707

hydrochloride + water binary mixtures are shown in figures 1 and 2 at different temperatures.

From table 6, figures 1 and 2, it can be seen that the limiting partial molar volume V_φ^0 are positive and increase with increasing temperature for the two systems examined. The positive values of V_φ^0 indicate that the solute–solvent interaction decreases as temperature increases.

The positive value of A_V for the two systems reveals stronger solute interaction. A_V decreases with an increase temperature, which is attributed to more violent thermal motion at higher temperature, resulting in diminishing force of the solute–solute interactions.

The variation of V_φ^0 with temperature can be expressed by the following equation [20,21]

$$V_\varphi^0 = \sum_{i=0}^{2} a_i T^i. \tag{8}$$

The values of the empirical constants a_0, a_1 and a_2 of equation (8) are given in table 7. The limiting partial molar volume expansibility $(\partial V_\varphi^0/\partial T)_P$can be obtained by differentiation of equation (8) with respect to temperature at constant pressure.

$$\left(\frac{\partial V_\varphi^0}{\partial T}\right)_P = a_1 + 2a_2 T. \tag{9}$$

Values of limiting partial molar volume expansibility $(\partial V_\varphi^0/\partial T)_P$ of cefepime hydrochloride are listed in table 6. It can be observed that $(\partial V_\varphi^0/\partial T)_P$ is positive over the temperature range under the investigation, and decreases with increasing temperature. This indicates that the interaction of molecules of cefepime hydrochloride between molecules of solvent decreases with increasing temperature. This phenomenon can be interpreted by the following reasons. The molecular thermal motion intensified with increasing temperature, and the interaction between molecules corresponding weakened, so the difference of solution structure and solvent structure decreases gradually.

For determining structure-making or structure-breaking capacities of cefepime hydrochloride in water or 0.9 mass % normal saline mixed solvents, following equation of Hepler [26] was used:

$$(\partial C_p/\partial p)_T = -T(\partial^2 V_\varphi^0/\partial T^2)_P. \tag{10}$$

The values of above term are summarized in table 7. According to Hepler criterion, structure-making solutes should have positive values and structure-breaking solutes, negative values. From table 7, that all $(\partial^2 V_\varphi^0/\partial T^2)_P$ are negative for cefepime hydrochloride in water or 0.9 mass % normal saline mixed solvents indicating structure-breaking tendency of cefepime hydrochloride in the present systems.

TABLE 9
Parameters of equation (13), together with correlation coefficient (R^2) and standard deviation (SD) for viscosity *B*-coefficient (*B*) in different systems from (278.15 to 313.15) K.

Systems	$10^2 \cdot A_1$	$10^3 \cdot A_2$	R^2	$10^6 \cdot \mathrm{SD/m^3 \cdot mol^{-1}}$
Cefepime hydrochloride + water	−371.9	15.27	0.996	3.77
Cefepime hydrochloride + 0.9 mass % normal saline	−85.48	8.060	0.987	5.51

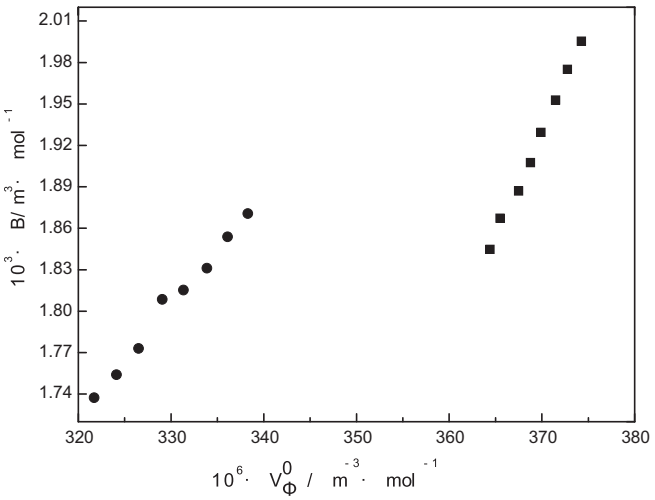

FIGURE 5. Plot of dependencies of the viscosity *B*-coefficient (*B*) on the standard partial molar volume (V_φ^0) for cefepime hydrochloride + water binary mixtures (■) and cefepime hydrochloride + 0.9 mass % normal saline ternary mixtures (•).

3.3. Relative changes in viscosity and viscosity B-coefficient

The relative changes in viscosity of cefepime hydrochloride in water or 0.9 mass % normal saline mixed solvents ($\Delta\eta$), can be expressed by following equation [27]

$$\Delta\eta = \frac{\eta - \eta_0}{\eta_0} = \frac{\eta}{\eta_0} - 1, \tag{11}$$

in which η and η_0 are the viscosities of solutions of cefepime hydrochloride in water or 0.9 mass % normal saline mixed solvents and pure solvents, respectively. $\Delta\eta$ is calculated from experimental data in tables 2 and 3 by equation (11). Some of the results are shown in figure 3. It can be seen that $\Delta\eta$ increases with increasing molarity of cefepime hydrochloride and decreases with increasing temperature, indicating solute–solvent interaction enhanced with increasing molarity of cefepime hydrochloride and weakened with increasing temperature. The thermal motion of the particles of the system increases with increasing temperature which leads the interaction of solute–solvent to be weakened. In the range of studied composition and temperature, $\Delta\eta$ are all positive. The results show that the intermolecular interactions increase when solution is formed, and indicate that there is negative deviation with Raoult's law.

The η/η_0 in equation (12) is relative viscosity (η_r) can be related to the solute concentration, c, according to the Jones–Dole equation [28,29].

$$\eta_r = \frac{\eta}{\eta_0} = 1 + A(c)^{1/2} + Bc, \tag{12}$$

where *c* is the molarity (calculated from molality) of the cefepime hydrochloride in the solution. Constant *B* is named as viscosity *B*-coefficient of solute. It represents coulombic interactions, size and shape effect of solute or Einstein effect, structural effect, and solvation effect caused by solute–solvent interaction [30]. It is a main contributor to η_r.

The values of *B*-coefficient obtained from experimental data by least-squares analysis are presented in table 8. The dependencies of relative changes in viscosity (η_r) on molarity cefepime hydrochloride (*c*) for cefepime hydrochloride + water binary mixtures are shown in figure 4. Data presented in table 8 and figure 4 show positive values of the *B*-coefficient for cefepime hydrochloride. This indicates the structure-breaking tendency of cefepime hydrochloride. The viscosity *B*-coefficient increases with increase of temperature, therefore, the values of dB/dT are positive. Usually, the dB/dT was known to be a better criterion for determining the structure-making/breaking nature of any solute, and for structure-making solute, the values are negative, for structure-breaking, positive. The positive values of dB/dT in the systems studied indicate that cefepime hydrochloride behaves as structure breaker, and solute–mixed solvent interactions destroy structure of solution, which is well consistent with the conclusion getting from volumetric properties of systems studied.

3.4. The relationship between the viscosity B-coefficient and the standard partial molar volume

The values of viscosity *B*-coefficient (*B*) and the standard partial molar volume (V_φ^0) of solute both can be used as measures of the solvation of solute or solute–solvent interaction. Therefore, there may be some relationship between the two thermodynamic parameters. In this paper, for the given system, the following relationship between the viscosity *B*-coefficient of solute and the standard partial molar volume can be obtained:

$$B = A_1 + A_2 V_\varphi^0, \tag{13}$$

where A_1 and A_2 are the parameters of equation (13), which were fitted by least square, and A_1, A_2 are listed in table 9 together with their standard deviations and the correlation coefficients. The plot of dependencies of the viscosity *B*-coefficient (*B*) on the standard partial molar volume (V_φ^0) for cefepime hydrochloride + water binary mixtures and cefepime hydrochloride + 0.9 mass % normal saline ternary mixtures are shown in figure 5. According to the formula [13], if the viscosity *B*-coefficient of solute in a solvent has been known, the standard partial molar volume can be calculated, and the reverse is also true. There is a similar relationship in ω-amino acids [31] and KSCN [32] aqueous solution. The A_2 value reflects the size and shape of the solute and lies between 0 and 2.5 for unsolvated spherical species [33]. For α-amino acids in water–sodium acetate mixtures, the researchers found that the increase in viscosity is predominately due to the increased resistance offered by the more structured solvent to the moving amino acid moiety, though solvation effects may also contribute [34]. The values of A_2 in table 8 showed that the cefepime hydrochloride molecules are unsolvated in the solutions.

4. Conclusions

The experimental densities and viscosities are determined for cefepime hydrochloride in water and 0.9 mass % normal saline from (278.15 to 313.15) K. From experimental measurements of densities and viscosities, apparent molar volumes, standard partial molar volumes, and the viscosity *B*-coefficient of cefepime

hydrochloride were calculated. The apparent molar volume not only increases with the increasing concentration of cefepime hydrochloride at a given temperature but also increases with increasing temperature. The positive values of V_{φ}^{0} indicate that the solute–mixed solvent interaction decreases as temperature increases. Positive values of the viscosity *B*-coefficient indicate the structure-breaking tendency of cefepime hydrochloride. The positive values of dB/dT manifest that cefepime hydrochloride behaves as structure breaker, and solute–solvent interactions destroy structure of solution, which is well consistent with the conclusion getting from volumetric properties of systems studied.

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References

[1] H.A. Zarei, F. Jalili, J. Chem. Thermodyn. 39 (2007) 55–66.
[2] S.S. Dhondge, S.P. Zodape, D.V. Parwate, J. Chem. Thermodyn. 48 (2012) 207–212.
[3] B. Sinha, B.K. Sarkar, M.N. Roy, J. Chem. Thermodyn. 40 (2008) 394–400.
[4] J. Barre, J. Antimicrob. Chemother. 26 (Suppl. C) (1990) 95–101.
[5] I.H. Patel, S. Chen, M. Parsonnet, et al., J. Antimicrob. Chemother. 20 (1981) 634–641.
[6] C. Jenna, J.W. Matthew, R.T. Charles, Crit. Rev. Toxicol. 40 (2010) 287–304.
[7] M. Isabel, C.L.-D. Juilo, R. Marta, et al., Environ. Toxicol. Chem. 28 (2009) 2706–2714.
[8] J.I. Muhammad, A.C. Mansoora, J. Chem. Thermodyn. 41 (2009) 221–226.
[9] A.H. Mutnick, P.R. Rhomberg, H.S. Sader, R.N. Jones, J. Antimicrob. Chemother. 53 (2004) 290–296.
[10] Y. Dafna, P. Mical, F. Abigail, S. Nadav, Lancet Infect. Dis. 7 (2007) 338–348.
[11] X.L. Zhou, B. Xiang, J.R. Gao, Handbook of Fine Chemical–Drug, Chemical Industry Press, Beijing, 2003.
[12] S.N. Timasheff, G.D. Fasman, Structure and Stability of Biological Macromolecule, Marcel Dekker, New York, 1969.
[13] W.P. Jencks, Catalysis in Chemistry and Enzymology, McGraw Hill, New York, 1969.
[14] J.M. Prausnitz, R.N. Lichtenthaler, E.G. Azevedo, Molecular Thermodynamics of Fluid-Phase Equilibria, third ed., Prentice-Hall PTR, Upper Saddle River, New Jersey, 1999.
[15] Y. Li, L. Xu, F.A. Wang, H.H. Jin, B.Z. Ren, J. Chem. Eng. Data 55 (2010) 4098–4103.
[16] The Minister of Health, Labour and Walfare, The Japanese Pharmacopoeia, 15th ed. (JP 15)., Society of Japanese Phamacoeia, Tokyo, 2007.
[17] J.A. Dean, Lange's Handbook of Chemistry, 15th ed., McGraw-Hill, NewYork, 1999.
[18] M. Kikuchi, M. Sakurai, N. Nitta, J. Chem. Eng. Data 41 (1996) 1439–1445.
[19] K. Toda, H. Furuse, J. Biosci. Bioeng. 102 (2006) 524–528.
[20] P. Zhang, F.A. Wang, J.Y. Wang, C.W. Li, B.Z. Ren, J. Mol. Liq. 42 (2008) 22–28.
[21] H. Shekaari, F. Jebali, J. Chem. Eng. Data 55 (2010) 2517–2523.
[22] X. Wang, F. Yang, Y. Gao, Z. Liu, J. Chem. Thermodyn. 57 (2013) 145–151.
[23] D.M. Bajić, G.R. Ivaniš, Z.P. Visak, Emila M. Živković, Slobodan P. Šerbanović, Mirjana Lj. Kijevčanin, J. Chem. Thermodyn. 27 (2013) 510–529.
[24] A. Pal, S. Soni, J. Chem. Eng. Data 58 (2013) 18–23.
[25] D. Warmińska, Carbohydr. Res. 349 (2012) 44–51.
[26] L.G. Hepler, Can. J. Chem. 47 (1969) 4613–4617.
[27] J.Y. Wang, F.A. Wang, P. Zhang, C.W. Li, B.Z. Ren, J. Chem. Eng. Data 53 (2008) 648–653.
[28] S.B. Tarlok, S. Harpreet, K.B. Parampaul, J. Chem. Eng. Data 55 (2010) 3872–3881.
[29] M. Huque, I.A. Siddiquey, M.N. Uddin, J. Chem. Thermodyn. 38 (2006) 1474–1478.
[30] T.S. Banipal, D. Kaur, P.K. Banipal, Z. Phys. Chem. 220 (2006) 1049–1069.
[31] E.L. Shock, H.C. Helgeson, Geochim. Cosmochim. Acta 54 (1990) 915–945.
[32] R.K. Wadi, R.K. Goyal, J. Solution Chem. 21 (1992) 163–170.
[33] R.H. Stokes, R. Mills, Viscosity of Electrolytes and Related Properties, Pergamon, London, 1965.
[34] Z. Yan, J. Wang, J. Lu, Biophys. Chem. 99 (2002) 199–207.

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